

## COMMENTARY

## A New Metric for Precision Medicine: PAP and Hypoglossal Neurostimulation

Commentary on Lee et al. Therapeutic positive airway pressure level predicts response to hypoglossal nerve stimulation for obstructive sleep apnea. *J Clin Sleep Med*. 2019;15(8):1165–1172.

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For many patients, a diagnosis of obstructive sleep apnea (OSA) results in a single treatment option of positive airway pressure (PAP) therapy, but PAP is not always accepted and long-term adherence to PAP is not achieved by a substantial percentage of patients.<sup>1</sup> The PAP-or-none approach has been gradually replaced by personalized treatment that includes oral appliances, modern upper airway surgery, positioning devices, weight loss, and—most recently—implantable hypoglossal neurostimulation (HGNS). To help match treatment modalities to patients, various phenotypes and endotypes such as loop gain, arousal threshold and anatomic burden have been identified but application of these measures is hampered by methodological complexity.<sup>2</sup> In this issue of the *Journal of Clinical Sleep Medicine*, Lee and colleagues have identified an alternative, readily available marker to better define treatment phenotypes using continuous positive airway pressure (CPAP) levels.<sup>3</sup> Conceptually, higher PAP levels may represent a higher critical closing pressure (Pcrit), a measure of upper airway anatomic burden.<sup>4,5</sup> Individuals without OSA (and a low anatomic burden) have Pcrit of 8 cmH<sub>2</sub>O or lower, while patients with OSA (with a higher anatomic burden) have Pcrit ranging from –4 to +4 cmH<sub>2</sub>O.<sup>6</sup> In a study by Landry and colleagues, patients with Pcrit ≤ –2 cmH<sub>2</sub>O required a mean PAP level of 6.2 cmH<sub>2</sub>O while those with Pcrit > –2 cmH<sub>2</sub>O had a mean PAP level of 10.3 cmH<sub>2</sub>O.<sup>10</sup>

HGNS has been shown to effectively reduce the apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and importantly, improve quality of life and self-reported sleepiness in feasibility, pivotal and clinical registry studies.<sup>7–9</sup> Despite HGNS application in a difficult, PAP non-adherent patient population, adherence mean for HGNS has been shown to be 5.7 h/night.<sup>10</sup> The challenge for this novel therapy is the identification of useful selection criteria for good outcome as rates for mean AHI reduction vary from 53% to 72% in clinical trials and registry studies. At present, selection for HGNS is largely based on body mass index (BMI), AHI and drug-induced sleep endoscopy (DISE) collapse pattern.<sup>11</sup> All three criteria are not particularly predictive. While most patients using HGNS implanted in clinical studies have had BMI < 32 kg/m<sup>2</sup>, a significant number of patients with lower BMI did not respond and some with higher BMI responded to HGNS. An AHI upper limit of 65 events/h

is somewhat arbitrary and not precise, as AHI is variably defined, is variably measured across sleep centers, and night to night in the same sleep center. DISE has been used for exclusion of patients who have a complete circumferential collapse (CCC) of the retro-palatal airway, as this pattern may indicate greater collapsibility. Unfortunately, there is variability in the performance and scoring of DISE, and some patients with the CCC pattern still appear to benefit from HGNS. Thus, the challenge remains for identification of better selection criteria and improved outcome.

In this issue of the *Journal of Clinical Sleep Medicine*, Lee and colleagues retrospectively assessed PAP treatment settings as a possible predictor of HGNS success. PAP treatment levels of 8 cmH<sub>2</sub>O and higher were noted to be associated with greater probability of lower HGNS responsiveness. The PAP settings analyzed were of heterogeneous sources, derived from best setting on CPAP titration studies, CPAP device levels, as well as the mean and median levels of auto-adjusting PAP devices. For auto-adjusting devices, the 90% or 95% treatment pressures would have been preferable to analyze, as they may be more similar to CPAP levels, although different manufacturers of PAP devices use different algorithms for pressure adjustment. The type of interface used for PAP was not determined, and this may also influence PAP setting, with oronasal interface use resulting in a higher PAP level as compared with nasal PAP interface. The above may partially explain why 40% of the patients treated with 8 cmH<sub>2</sub>O PAP or greater still responded favorably to HGNS, or perhaps the 8 cmH<sub>2</sub>O cutoff is artificially low. The small sample size warrants additional studies to confirm the findings, especially as the “low PAP” group represented only a quarter of the patients. In addition, ODI data should have been reported for all patients, as ODI is more reliably measured than the AHI.

For oral appliance therapy (OAT), PAP levels have also been correlated in several studies with favorable outcome.<sup>12–15</sup> In some of the studies, a level of 8 cmH<sub>2</sub>O or lower was favorable and in others, a level of 12 cmH<sub>2</sub>O or lower was favorable. The studies differ significantly with respect to ethnicity of population, BMI, OSA severity, PAP setting determination method, oral appliance used and advancement scheme. Nonetheless the 12 cmH<sub>2</sub>O or lower criteria is reasonable given the range of Pcrit levels in patients with OSA and that

pressure differential of 8 cmH<sub>2</sub>O from the critical pressure is needed to treat most patients with OSA. Additional predictors for successful OAT are needed, and one may be awake fiberoptic endoscopy findings with mandibular advancement. In a prospective study of patients with severe OSA, the cross-sectional area increase in the velopharynx with mandibular protrusion was associated with successful AHI outcome, having an 86% positive predictive value and 81% negative predictive value.<sup>16</sup>

What is the linkage between a low PAP therapeutic setting and clinical outcome with HGNS and OAT? Although initially conceptualized as therapies directed at the tongue base, both OAT and HGNS are currently believed to function via their effects on the soft palate and pharyngeal walls. The data from the current study suggests that if the effective PAP level is related to Pcrit measures, then it is those patients who have a lower anatomic burden that are best suited for this type of monotherapy. Since many patients with OSA currently use pressures greater than 8 cmH<sub>2</sub>O, a better understanding of the link between structure, PAP, and airflow may identify methods to increase effectiveness of HGNS. Future directions may include bilateral hypoglossal neurostimulation, improved stimulation timing schemes or more precise muscular activation for improved upper airway patency. Further research probing the dynamics how PAP alters different patterns and shapes of flow limitation may provide insight into these questions. The work of Lee et al<sup>3</sup> supports that available metrics such as PAP pressure may assist sleep practitioners to better identify patient phenotypes and personalize care.

## CITATION

Jacobowitz O, Woodson BT. A new metric for precision medicine: PAP and hypoglossal neurostimulation. *J Clin Sleep Med*. 2019;15(8):1079–1080.

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## SUBMISSION & CORRESPONDENCE INFORMATION

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## DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Dr. Jacobowitz is a scientific advisor to ImThera Medical/LivaNova and a consultant for Nyxoah Medical. Both companies developed hypoglossal neurostimulation systems that received Conformité Européenne (CE)-mark but are investigational in the USA. Dr. Woodson is a consultant for Inspire Medical Systems whose hypoglossal neurostimulation system is FDA-approved in the USA.